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I also certify that by virtue of an assignment registered under the Patents Act 1977, the application is now proceeding in the name as substituted.

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Signed R. Mahoney

Dated 2 February 2000

GB9828696.6

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

TAYSIDE UNIVERSITY HOSPITALS NHS TRUST
Ninewells Hospital & Medical School
DUNDEE
DD1 9SY
United Kingdom

[ADP No. 07780828001]

Patents Form 1/77

Patents Act 1977
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference

M98/0481/GB

2. Patent application number
(The Patent Office will fill in this part)

9828696.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

J Graeme HOUSTON
Bishops House
Fairmount Road
Perth PH2 7AW

John DICK
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Perth PH2 7AW

SECTION 30 (1977 ACT) APPLICATION

Patents ADP number *(if you know it)*

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Bishops House
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If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Blood-Flow Tubing

5. Name of your agent *(if you have one)*

McNeight & Lawrence

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Regent House
Heaton Lane
Stockport
Cheshire
SK4 1BS

Patents ADP number *(if you know it)*

0001115001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

No

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	7
Claim(s)	2
Abstract	1
Drawing(s)	2 + 2

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature McNeight & Lawrence Date 24.12.98

12. Name and daytime telephone number of person to contact in the United Kingdom David L McNeight 0161 480 6394

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BLOOD-FLOW TUBING

This invention relates to artificial or modified natural blood-flow tubing, by which is meant artificial vascular prostheses or modified natural grafts of autografts, and tubing in which blood flows outside the body e.g. in dialysis or in open heart surgery. Indeed, the invention might well extend to any tubing that carries a laminar flow, and particularly, but not exclusively, a pulsatile flow.

Spiral flow has been observed (Stonebridge P.A., Brophy C.M., Spiral laminar flow in arteries?, Lancet 1991; 338 : 1360-61) during angioscopy, as has the presence of spiral folds on the endoluminal surface of blood-vessels. The observation, it was said could have been an artefact of angioscopy, or the phenomenon may occur only in diseased arteries because of turbulence generated atherosclerosis, or it may be physiological, the latter having some support from other observations of rotational flow.

Indeed, in this seminal article, it is remarked that, if confirmed, the existence of spiral rather than laminar blood flow in peripheral arteries would have striking implications for the understanding of haemodynamics, arterial wall function, the pathogenesis of a atherosclerosis and intimal hyperplasia, and the design of prosthetic graft materials.

Confirmation came with the publication by Stonebridge and others of a paper "Spiral laminar flow *in vivo*" in Clinical Science (1996, 9), 17-21 in which, using standard colour flow Döppler techniques, velocity information, a rotational element to forward flow during all or part of the pulse cycle was demonstrated in each of eleven healthy male volunteers.

However, even with this confirmation, it was admitted that it had not yet been shown whether angioscopic observations of a spiral pattern on the endoluminal surface of arteries and spiral flow patterns were real events or observational artefacts.

More recent work with magnetic resonance imaging ("MRI") has established, however, that rotational flow is beneficial at least in certain situations and is presumed, on that account, to be "selected for".

The prediction, therefore, by Stonebridge and Brophy in the 1991 Lancet report is vindicated, though it has only now become apparent just how to design prosthetic graft materials in order to reproduce, or at least not to destroy, the physiological rotation, and not at the same time bring about any disadvantages. It has also become apparent that the findings are of interest in connection with blood flow tubing other than grafts, and possibly, indeed, with other tubing as well.

The invention comprises, in one aspect, tubing, especially, but not exclusively artificial or modified natural blood flow tubing having helical-flow inducing means adapted to induce helical flow in such fashion as to eliminate or reduce turbulence.

The tubing may have internal helical grooving and/or ridging, which may be multi-start grooving and/or ridging. The grooves and ridges may be of any cross-sectional shape and size, for example semi-circular, square, triangular or sinusoidal - some may be found more effective than others in particular circumstances.

By "helical" as used herein is meant "generally helical", rather than always mathematically precisely helical.

Instead of, or in addition to grooving and/or ridging, the tubing may be of non-circular cross-section, twisted. Synthetic or other thermoplastic or plastifiable and re-settable material made as a straight, circular or non-circular cross-section tube, may be plastified and reset in twisted condition.

The helical formation may have a constant helix angle along at least a part of its length, or one which reduces or increases over at least part of its length. The grooving and/or ridging, where present, may taper in the direction of flow or in the opposite direction.

The helical flow inducing means may comprise a bio-compatible insert, which may comprise helical vane means, which may, for example, be fashioned like fan or propeller blades or which might be elongated spiral projections from the inner surface of a cylindrical insert.

The tubing may have a branched structure in which the flow is from a first branch into two second branches in which helical-flow inducing means are provided where the tubing branches so as to eliminate or reduce turbulence downstream from the first branch. The same may be provided for confluent branches, of course.

The invention also comprises a method for making blood flow tubing comprising forming the tubing on a mandrel which has helical grooving and/or ridging at least over part of its length. The tubing may be formed, for example, by coagulation casting. In another method, a non-circular section tube may be formed with a twisted cross-section either directly on a mandrel itself having a twisted non-circular cross-section or by making a tube with non-circular, non-twisted cross-section and then twisting, plastifying and re-setting the tube in the twisted configuration.

Tubing made as described may be adapted for use as a vascular prosthesis for implanting into the human or animal body. After-care may involve confirming the helical-flow inducing effect of implanted tubing by measurement of a rotational component of flow, e.g. by MRI, or Döppler ultrasound.

A method for use in designing tubing for implant in various locations in the cardio-vascular system may, according to the invention, involve taking measurements of rotational flow in such locations, as by MRI, in a healthy population in order to determine a typical flow, and designing tubing adapted to produce such flow in such locations. The design may be by mathematical modelling or by trial and error (*ex vivo*, preferably), with, perhaps, "fine tuning" by after-care measurement comparing predicted with actual flows to improve subsequent prostheses.

It is also possible, according to the invention, that intravascular stents inserted e.g. during angioplasty procedures, could have spiral-flow inducing properties.

Where an insert is used which is accessible, e.g. during angioscopy, it may be made adjustable, for example its helix angle may be increased or decreased by extending or contacting a flexible vane arrangement on a rigid support, and this may be done during angioscopy with simultaneous measurement of the rotational component of flow produced by the insert, whereby to achieve a desired flow.

Tubing according to the invention may, however, be adapted for use in or with blood treatment or delivery equipment, such as a heart-lung machine, dialysis equipment or a giving set.

Embodiments of tubing and methods of making and using the same will now be described with reference to the accompanying drawings, in which:

Figure 1 is a perspective view of a short length of tubing of a first embodiment settable for prosthetic implant in a cardio-vascular system;

Figure 2 is a cross-section of a second embodiment of tubing;

Figure 3 is a perspective view of a third embodiment;

Figure 4 is a view of the inside of a length of tubing, opened out;

Figure 5 in an elevation of a mandrel for use in casting tubing according to the invention;

Figure 7 is a view of a vaned device in a tube; and

Figure 9 is a view of a branched tube according to the invention.

The drawings illustrate blood-flow tubing 11 having helical-flow inducing means 12 adapted to induce helical flow in such fashion as to eliminate or reduce turbulence. The tubing may be artificial, for example woven or knitted synthetic polymer fibre, in which the helical-flow inducing means may be knitted or woven structure as by three dimensional knitted or woven formation, or extruded or cast tubing, or modified natural, e.g. autograft material with an insert or with grooving made e.g. by a laser.

The helical-flow inducing means 12 may comprise grooving 14 and/or ridging 15, which may be multi-start grooving and/or ridging as seen in Figures 1, 2 and 4. Square-section ridging, as seen in Figure 1, or grooving, or semi-circular section

ridging and/or grooving, as seen in Figure 2, can be used, but other cross-sections will service as well, for example, triangular.

However, as seen in Figure 3, a non-circular section tube 11 can have a twist, and may also have internal ridging and/or grooving. A twisted tube may be cast as such on a twisted mandrel or, if, for example, of thermoplastic material, may be twisted and heat-set in that state.

The helical-flow inducing means may extend over the whole length of the tubing. It seems, on present knowledge, to be important at least to provide it where turbulence is likely to occur, for example at the inlet or outlet from the tubing, or in branched tubing as seen in Figure 9, where turbulence can be occasioned in the branch region and can be controlled by ridging and/or grooving 12 at the inlets to the two minor branches 11b where they join the main branch 11a, and/or in the main branch 11a itself. It may be found desirable to have different ridging and/or grooving in the two minor branches, where, for example, they run at different angles to the main branch.

It may be arranged that the ridging and/or grooving 12 has a reducing helix angle in the flow direction over at least part of its length - this is illustrated in Figure 4, where the grooving 12 is also tapered so as to extend only over an inlet region L, but the tapering and reducing angle could extend over longer lengths of tubing. The opposite - helix angle increasing and/or depth of grooving or height of ridging increasing in the flow direction may also be appropriate in some circumstances.

Figure 5 is an elevation of a mandrel 51 such as may be used in a coagulation casting process to make prosthesis of polyetherurethane or other biocompatible polymer. Grooves 52 are provided on the mandrel 51 which then forms a tube with internal ridging.

Figures 7 and 8 illustrate helical vane devices 71 which can be inserted in tubing to cause helical flow. In Figure 8 the effect can be increased by a probe 81 as used in angioscopy. The vanes 82 are on a sleeve 83 and sufficiently flexible to be compressed on a rigid support 84 by a sleeve 85 of the probe 81 being advanced relative to a core 86, the core 86 engaging the support 84 while the sleeve 85 is advanced against the sleeve 83, the sleeve 83 being held in the compressed state by a ratchet arrangement 87 between support 84 and sleeve 83. Such a device may be adjusted during angioscopy while observing the rotational flow induced, thereby, e.g. by MRI. The adjustment may be effected in any other fashion, e.g. by the application of torque to one end while holding the other end fixed.

It is noted that the mere provision of helical flow induction will not necessarily reduce or eliminate turbulence. It will be important to select the most appropriate configuration, which may well be done by trial and error. It may, of course, be found, especially where sharp bends or corners are encountered in the tubing that there is a limit to the stability of rotational flow - it may be necessary, if possible, to refashion the tubing to eliminate sharp bends or corners before helical flow will have the effect of inducing or maintaining non-turbulent flow.

Designs for the tubing and methods for making the same other than those already discussed can of course be envisioned, as can other ones, all falling within the scope of the invention.

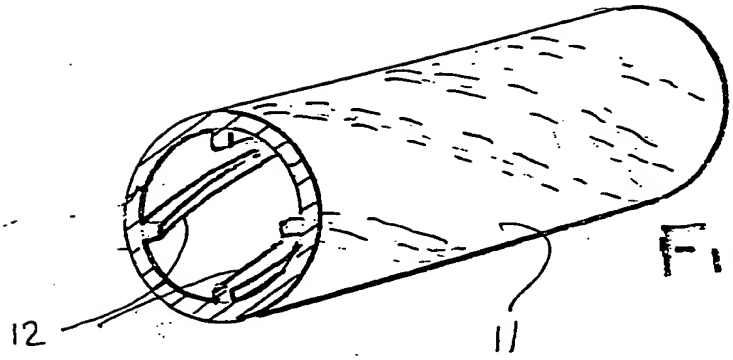

Fig 1

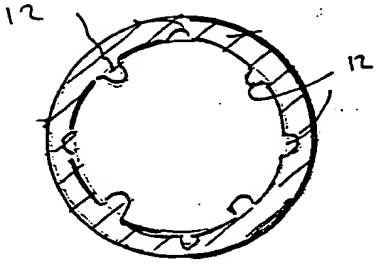

Fig 2

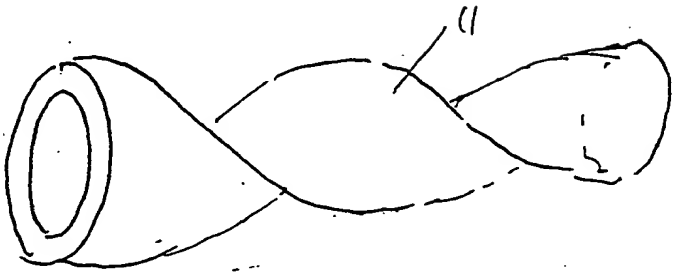

Fig 3

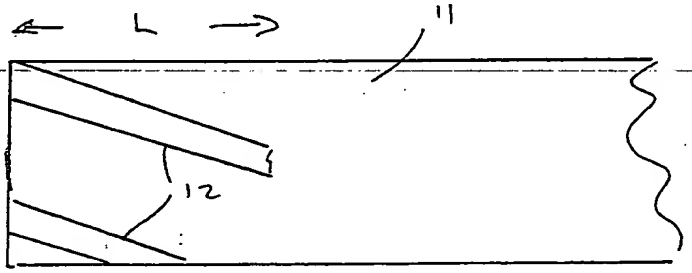

Fig 4

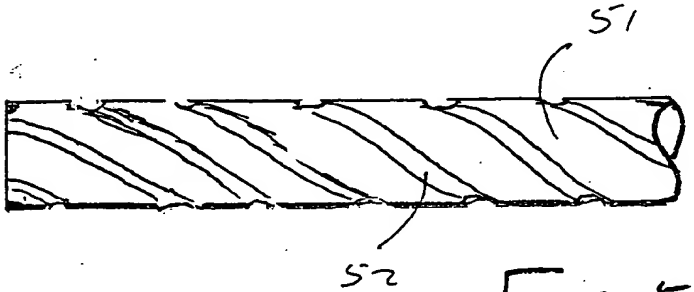

Fig 5

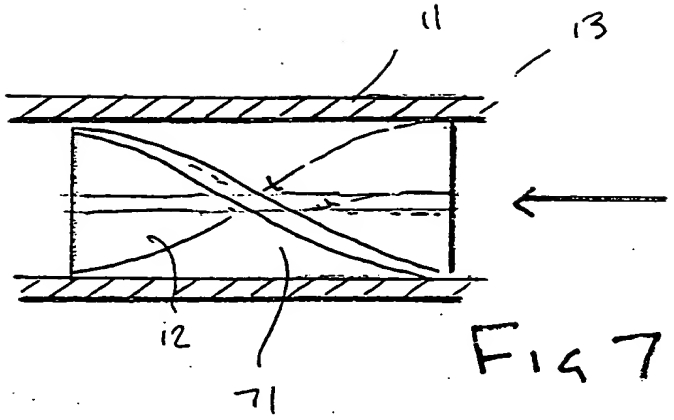

Fig 7

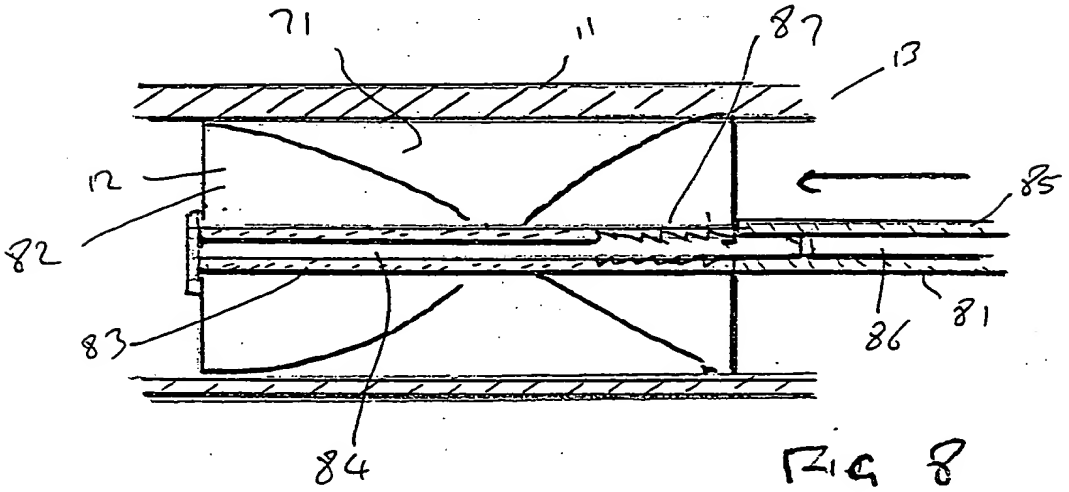

Fig 8

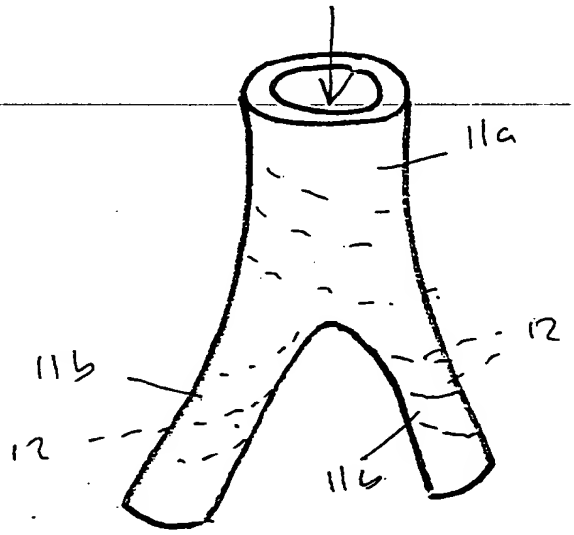

Fig 9.

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Mr Neight & Lawrence